EDITORIAL COMMENT

In Search of an Algorithm to Prevent Acute Kidney Injury*

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In this issue of JACC: Cardiovascular Interventions, Brown et al. (1) present a meta-analysis of 10 trials involving combined therapy with sodium bicarbonate (NaHCO₃) plus N-acetylcysteine (NAC) and demonstrate a significant reduction in acute kidney injury (AKI) with this regimen as compared with other prophylactic strategies. Given that the risk of contrast-induced AKI in high-risk patient groups might exceed 20% (2,3) and that AKI is associated with considerable morbidity (4), a simple strategy for AKI prophylaxis could potentially lead to significant quality improvement across cardiovascular catheterization laboratories. The authors conclude: “We recommend that a comprehensive prophylactic protocol needs to be incorporated into practice to prevent contrast-induced AKI, incorporating both NaHCO₃ and NAC.” The precedent for a clear-cut algorithm for care to improve outcomes has been established for interventional cardiology most notably with respect to primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Are we now ready to bring that same kind of clarity to an algorithm to prevent contrast-induced AKI?

Where Consensus Rests

The need for ongoing meta-analyses of therapies to prevent contrast-induced AKI might be inexorably linked with a feeling that no single trial provides a clear path. Although it is true that this field lacks a single mega-trial on which an algorithm can be based, there are real insights over the past 2 decades that could be adhered to in clinical practice. First, there are agents that simply do not work: calcium channel blockers, dopamine, mannitol, furosemide, and intravenous fenoldopam.

In contrast, hydration clearly does work, and all patients at risk for AKI should undergo volume expansion (3,5).

What is the optimum method of volume expansion: NaHCO₃ for 7 h or normal saline for a minimum of 12 h? The current meta-analysis might help us with this particular question. Although the report focuses conclusions on “combination prophylaxis,” it is possible this report might fall into the simpler category of “bicarb is better” (6,7). There are 10 trials included in the current meta-analysis, with a total of 21 treatment regimens being compared. Of these 21 treatment regimens, all 21 include some form of NAC. Conversely, 10 trials include NaHCO₃, whereas 11 trials include intravenous hydration with normal saline. Thus, hydration method is the only true variable. Elementary school math suggests that the meta-analysis might be presenting the following equation for the rate of contrast-induced AKI:

Bicarbonate + NAC < normal saline + NAC
Subtract NAC from both sides of the equation
Bicarbonate < normal saline

This becomes fuzzy math only if we assume that a background of NAC is differentially required to potentiate the benefits of NaHCO₃ as opposed to normal saline. Because there is no evidence to support this concept to date, it seems more likely that the current meta-analysis extends the conclusions of prior meta-analyses, suggesting that NaHCO₃ is the current best regimen for volume expansion (6–8). Although there are contradictory trials with respect to bicarbonate superiority (9), the clinician might be comforted by the following practical points: 1) even when clinical trials have failed to show superiority of NaHCO₃, they have yet to show evidence of any harm; 2) it is much easier to give 1 h of NaHCO₃ before procedure plus 6 h of post-procedure NaHCO₃ than any of the regimens with normal saline that require 12 to 24 h of infusion; 3) replacing normal saline as the volume expander of choice has no cost implications to your institution; and 4) advocates of NaHCO₃ for AKI prophylaxis are not financially motivated—there are no industry ties related to prophylactic salt administration.

Where Controversy Remains

Are the authors correct that NAC should be a mandatory part of all algorithms for AKI prophylaxis? A missing arm of this meta-analysis is needed to provide more convincing evidence—the arm with NaHCO₃ alone versus NaHCO₃ plus NAC. NAC is a potent antioxidant with real effects on myocardial salvage and renal cell injury in our porcine models (10). But, the results of individual trials and meta-analyses of NAC in human studies of AKI have been very mixed. At least 9 meta-analyses of NAC benefit have been published to date, and the results of these meta-analyses are inconsistent with respect to a clear benefit of NAC (3,4,11).

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In contrast, almost all analysis of NAC is unified with respect to heterogeneity: no one knows the optimum dose or route of administration—oral (12), intravenous (13), or intracoronary (10)—and thus the grouped NAC trials are difficult to analyze (14).

There are practical aspects of NAC administration that might help inform the creation of an algorithm. First, NAC has not been associated with any clear harm: thus, erring on the side of NAC use would not be expected to worsen outcomes. Second, NAC also has no real side effects other than the awful taste of the oral formulation. Third, the most common dose used is 600 mg orally twice daily the day before and the day of the procedure: for outpatients undergoing elective cardiovascular procedures, this requires a separate trip to the pharmacy to obtain a bad-tasting medication. For inpatients, the ability to administer any drug over 24 h before invasive procedures is limited by the urgency of the procedure. Although some studies have attempted to overcome this barrier with intravenous (13) or abbreviated regimens of NAC (15), the results of these trials (like all other trials of NAC) have been conflicting (5). Thus, unlike the bicarbonate versus saline comparison, the NAC versus placebo comparison unfortunately rests firmly at equipoise and uncertainty.

**An Algorithm for Care**

The lack of certainty regarding NAC does not negate the important observations of the current meta-analysis or the significant contributions of investigators who have highlighted the need to prevent AKI. Rather, the consistency of findings with respect to: 1) AKI incidence, predictors, and outcomes; and 2) volume expansion, particularly with NaHCO₃, as a meaningful prophylaxis regimen brings potential for initiation of a uniform algorithm for care. In July 2007, we anticipated the authors’ current recommendation: “We encourage institutions to form a multidisciplinary team . . . to work together to develop evidence-based benchmarks for high-quality care and standardize their prophylactic strategies in preventing contrast-induced AKI.” Through meetings with Dr. Richard Solomon, our Chief of Nephrology, we created a “best practices” algorithm to prevent AKI and made this a single, universal approach used by every attending physician in our cardiovascular catheterization laboratory (Fig. 1).

What did we do in 2008 when a new trial was published suggesting that “bicarbonate is not actually better” (9)? Rather than change the algorithm, we looked at 2 factors: 1) did the trial show any negative correlates of continuing our current practice (no)?; and 2) did we expect better compliance by potentially switching between equivalent regimens on a yearly basis (no)? Thus, our practice continues what the authors propose in this meta-analysis, with the lack of a firm commitment to NAC. Furthermore, AKI prophylaxis algorithms need to incorporate other factors that might contribute to patient dehydration (no more “NPO after midnight”) or renal injury (stop the nonsteroidal anti-inflammatory drugs). And, finally, like all successful algorithms, it is a simplified representation of the published data: although there are many other risk factors for AKI, we sought 100% compliance with this regimen with respect to 1 main factor (creatinine clearance) rather than a host of variables (acute infarction, heart failure, diabetes) that might create memory challenge.

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**Figure 1. A Sample Algorithm to Address Acute Kidney Injury in Cardiovascular Catheterization Laboratories**

CHF = congestive heart failure; GFR = glomerular filtration rate; NPO = nothing by mouth; NSAIDs = nonsteroidal anti-inflammatory drugs.
Is the University of Vermont approach correct or complete? There is more than 1 correct algorithm for preventing AKI, and the gray areas dictate a reasonable variability in approaches. And clearly there is room for ample discussion regarding choice of contrast agents to reduce the occurrence of AKI (3). But the current meta-analysis states that it is time for all institutions to both measure AKI and institute some form of quality improvement program to address AKI with an algorithm for prophylaxis. Our experience suggests that this is a correct statement. Our incidence of AKI among our PCI patients was 4.6% in 2003. By the end of 2008, we had achieved our lowest incidence of AKI to date—approximately 2.0% (David Malenka and Winthrop Piper from the Northern New England Cardiovascular Study Group, personal communication, July 7, 2009). Thus, the current meta-analysis might not clearly demonstrate the absolute requirement for “combination therapy”; however, the concordance of meta-analyses on volume expansion brings to the forefront a new ST-segment elevation myocardial infarction-like area for quality improvement: the potential to create a uniform institutional algorithm for care of patients at risk of AKI.

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REFERENCES


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